An Update of Vitamin B_{12} Metabolism and Deficiency States

Randall Swain, MD
Charleston, West Virginia

Vitamin B_{12} deficiency may be underestimated in the general population. High-risk groups for the deficiency syndrome include the elderly, patients taking ulcer medications over long periods, patients with acquired immunodeficiency syndrome, vegetarians, patients who have undergone stomach resection or small bowel resection, or both, and patients with dementia.

The vitamin B_{12} deficiency syndrome is characterized by five stages, the fifth of which results in irreversible neuropsychiatric manifestations. Although the deficiency is easily treated, diagnosis is somewhat complicated by the shortcomings of the various tests. Current state-of-the-art testing uses serum cobalamin levels as a screening test and serum or urine homocysteine and methylmalonic acid determinations as confirmatory tests. Vitamin B_{12} deficiency is treatable with monthly injections, large doses of daily oral supplement tablets, or an intranasal gel, which is far better absorbed than comparable oral supplements.

Key words. Vitamin deficiency; vitamin B_{12}.
(*J Fam Pract 1995; 41:595-600*)

Since the discovery of vitamin B_{12} in 1948, physicians have been aware, at least to some extent, of its importance to the human body. Today, as medical research focuses increasingly on vitamins, the importance of B_{12} is becoming even clearer. This review includes information on vitamin B_{12} deficiency, changing options in laboratory testing for deficiency states, and both old and new options for treatment.

A dietary cause of vitamin B_{12} deficiency is extremely rare except in those not eating well because of illness or age and in vegetarians, as vitamin B_{12} is found in abundance only in animal products. Since it is produced by microorganisms, it would be found only in small amounts in plants such as legumes that are contaminated with these microorganisms.

The vitamin is protein-bound in food and is separated from the protein complex by pepsin in the presence of stomach acid. It is then bound by intrinsic factor and transported from the proximal ileum to the distal ileum, where it is then bound to transcobalamin II for transport to the liver and bone marrow.

The recommended daily allowance (RDA) of vitamin B_{12} is 2 μg/d in the average adult, and the average daily intake is between 6 and 7 μg/d.[1] The body stores 2 to 5 mg of the vitamin, 50% of which is stored in the liver.[2]

Incidence

Investigators have estimated that 5% to 10% of persons over the age of 65 years are vitamin B_{12}–deficient.[3,4] With newer and more sensitive tests available, however, deficiency states have been found in as many as 15% to 20% of this population.[5,6] Since many elderly adults are not tested until there is evidence of macrocytic anemia, the true incidence may actually be unknown. Other populations at risk for vitamin B_{12} deficiency include vegetarians, patients who have undergone partial or total stomach resection (such as the Billroth procedures) or small bowel resection, and those at risk for dietary deficiencies due to alcohol abuse.

Submitted, revised, June 27, 1995.

From the Department of Family/Sports Medicine, West Virginia University–Charleston Division, Charleston. Requests for reprints should be addressed to Randall Swain, MD, Family/Sports Medicine, West Virginia University–Charleston Division, 1201 Washington St East, Suite 108, Charleston, WV 25301.

ISSN 0094-3509

Table 1. Neuropsychiatric Manifestations of Vitamin B_{12} Deficiency

Peripheral nervous system involvement. Symmetric peripheral neuropathy, beginning with symmetric parasthesias of the lower extremities, can ascend to eventually involve the upper extremities; hyporeflexia may be present; occasionally autonomic neuropathy occurs, which can present as orthostatic hypotension.
Spinal cord involvement. Dorsal column involvement: loss of position and vibration sense, ataxia, broad-based gait, and, occasionally, Lhermitte's sign. Lateral column involvement: weakness and spasticity (spastic paraparesis), urinary and fecal incontinence, impotence, hyperreflexia, clonus, and Babinski reflex may be present.
Subacute combined degeneration. Spinal cord involvement and peripheral neuropathy.
Visual impairment. Retrobulbar neuritis, optic atrophy, and pseudotumor cerebri.
Psychiatric manifestations. Dementia, hallucinations, frank psychosis ("megaloblastic madness"), paranoia, depression, violent behavior, and change in personality.

From Clementz GL, Schade SG. The spectrum of vitamin B_{12} deficiency. Am Fam Physician 1990; 41(1):150–62. Reprinted with permission of the American Academy of Family Physicians.

Clinical Information

Patients who are vitamin B_{12} deficient often present with nonspecific findings, such as anorexia, apathy, dyspnea, dizziness, glossitis, or fatigue.[3] Neuropsychiatric symptoms, which predominate, are listed in Table 1.[7] Studies have shown that these most often include symmetric paresthesia or weakness in the extremities, diminished vibratory sense, ataxia, memory loss, personality change, or hallucinations.[8]

Vitamin B_{12} deficiency is thought to be a continuum with five stages.[9] These stages include: I, normality; II, negative vitamin B_{12} balance; III, vitamin B_{12} depletion with possible clinical signs and symptoms (reversible neuropsychiatric findings); IV, vitamin B_{12}–deficient erythropoiesis with possible clinical signs or symptoms (potentially reversible neuropsychologic symptoms); and V, vitamin B_{12} deficiency anemia with probable clinical signs and symptoms, including irreversible lateral column involvement.

Pernicious anemia is the most common cause of vitamin B_{12} deficiency.[3,10] This problem is thought to be an autoimmune phenomenon involving the formation of antibodies against gastric parietal cells and intrinsic factor. Achlorhydria or decreased stomach acid results from atrophy of parietal cells, and there is decreased absorption of vitamin B_{12} due to decreased amounts of intrinsic factor and a nonacidic medium.[11] Diagnostic criteria for pernicious anemia may include low or borderline vitamin B_{12} levels, the appearance of antiparietal cell or anti-intrinsic factor antibodies in the blood, macrocytic anemia, hypersegmented neutrophils, and a positive result on the first part of the classic Schilling test.

Diagnostic Testing

Serum vitamin B_{12} levels were considered quite specific for deficiency until the late 1970s, when the Food and Drug Administration formed a committee to critically evaluate these assays. It was later found that early assays overestimated actual vitamin B_{12} levels owing to the measurement of nonactive cobalamin analogues. Although this problem has been addressed by newer testing methods, recent studies have shown that a significant number of patients with borderline serum levels may actually be vitamin B_{12} deficient.[5] Some asymptomatic patients may have borderline or even subnormal levels. Recent studies have shown that serum vitamin B_{12} levels decline 18 to 28 pmol/L annually in the normal elderly patient.[12] Therefore, confirmatory testing seems to be a prudent step, especially for the slightly low or borderline levels. Serum vitamin B_{12} should possibly be considered a screening test, with high levels ruling out a vitamin B_{12} deficiency, levels between 150 and 350 pmol/L requiring confirmation, and levels lower than 150 pmol/L probably not needing confirmation. Allen and colleagues[13] have found that serum methylmalonic acid (MMA) and serum homocysteine are two valuable markers for vitamin B_{12} defi-

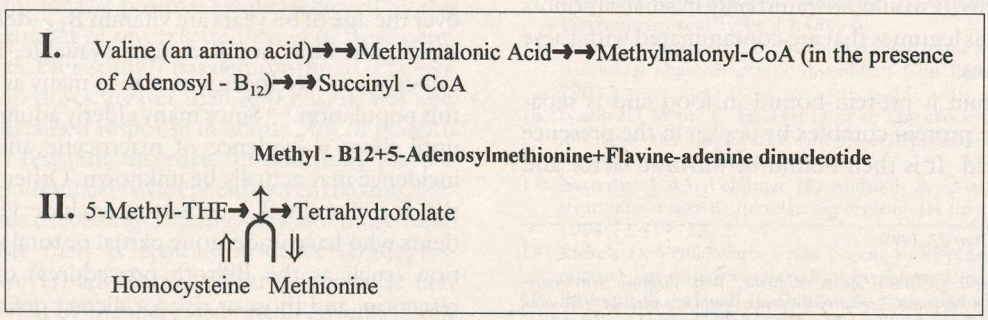

Figure. Enzymatic reactions dependent on the presence of vitamin B_{12}.

ciency. As there are only two biochemical pathways that utilize this vitamin in humans (Figure), these metabolites may accumulate in the blood stream resulting in elevated levels. Unfortunately, in most hospitals only a spot urine test for homocysteine and a 24-hour urine collection for testing MMA are available, at an average cost of $18.25 and $58 per test, respectively. Serum levels for homocysteine and MMA may be more specific but are available only through regional sites and, at an average cost of $125 per test, are much more expensive (Table 2). Savage et al[14] have shown that elevated levels of MMA are 96% to 99% accurate as an indicator for cobalamin deficiency. Only 7 of 434 cobalamin-deficient patients tested showed normal levels of MMA; 6 of these 7 had elevations in homocysteine levels. Therefore, if both homocysteine and MMA levels are elevated and the serum vitamin B_{12} level is low or borderline, vitamin B_{12} deficiency exists. If the homocysteine level is the only elevated metabolite and the red blood cell folate level is not low, vitamin B_{12} deficiency also may be indicated. Since elevated levels of homocysteine may also indicate a folic acid deficiency, however, red blood cell folate levels should be determined before vitamin B_{12} replacement is begun. It is important to ensure there is no cobalamin deficiency before starting folic acid replacement, as this therapy may worsen the associated neurologic symptoms.

Table 2. Diagnostic Tests for Vitamin B_{12} Deficiency

Diagnostic Test	Indications	Usual Cost
Serum B_{12} level	B_{12} deficiency	$39
Serum MMA and serum homocysteine	B_{12} and/or folate deficiency	$125 (per test)
Spot urine test for homocysteine	Possible B_{12} or folate deficiency	$18
24-hour urine collection for MMA	B_{12} deficiency	$58
MCV > 115 fL	Possible B_{12} or folate deficiency	$15
Peripheral smear/CBC	Hypersegmentation of neutrophils	$15
Antibodies to parietal cells and intrinsic factor	Pernicious anemia	$78.50 (per test)
Serum gastrin levels	Possible B_{12} deficiency	$38
Shilling test	B_{12} deficiency (14% false positives; 32% equivocal results)	$300 plus radiation exposure

MMA denotes methylmelonic acid; MCV, mean corpuscular volume; CBC, complete blood count.

Hematologic abnormalities are often associated with vitamin B_{12} deficiency but may be absent even when a significant deficit exists. In fact, the mean corpuscular volume (MCV) does not rise until stage IV of the process. Lindenbaum et al[8] showed that 14% of their study population had neither macrocytosis nor anemia after vitamin B_{12} deficiency was diagnosed. When present, macrocytosis (large red cells) is a nonspecific indicator of vitamin B_{12} deficiency. Although liver disease and alcohol use may also cause this finding, values of MCV greater than 115 fL are unusual except for vitamin B_{12}- or folate-deficiency states.[15] Another finding may be hypersegmentation of neutrophils on a peripheral smear. However, since these are now often interpreted only by automated cytometry, this information may not be readily available.

Tests for antibodies to parietal cells and intrinsic factor also may be ordered. These are present in the majority (90%) of cases of pernicious anemia but are also present in atrophic gastritis without pernicious anemia[16,17]; however, the absence of these markers does not rule out possible vitamin B_{12} deficiency. Serum gastrin levels may also be a helpful marker when interpreting an equivocal vitamin B_{12} level. Studies have shown that serum gastrin levels are elevated in 70% to 100% of patients with vitamin B_{12} deficiency.[18,19] Other pathologic conditions, including the Zollinger-Ellison syndrome and gastrin-producing tumors, may produce a positive test result. The cost of the serum gastrin test ($38) is reasonable, however, and the test is readily available.

Another diagnostic test that had been used exclusively in past years is the Schilling test. In the first stage of the test, the patient is given radiolabeled (cobalt 57) vitamin B_{12} orally, followed by a flushing dose of intramuscular vitamin B_{12} 1 to 2 hours later. Radioactivity is then measured in the urine. Stage II consists of repeating the test with intrinsic factor also being administered. Normal results on stage II, but not stage I, indicate that vitamin B_{12} deficiency is probably due to intrinsic factor deficiency. Problems with this test include a 14% chance of false positives,[3] a 32% chance of equivocal results, and a relatively high cost (approximately $300) in nuclear medicine departments. Some hospitals have stopped performing this test. Lindenbaum and associates[8] have found that up to 25% of patients with pernicious anemia will still have low results on stage II for 2 months after vitamin replacement has begun owing to problems in the absorption of the intrinsic factor–vitamin B_{12} complex. Another limitation of this test is that some patients have problems absorbing the vitamin in its protein-bound state. Therefore, this test has limited value.

Testing for vitamin B_{12} deficiency in patients with compatible neurologic symptoms or macrocytosis is begun with a serum level. If necessary, serum or urine levels

of MMA and homocysteine should be used to determine the significance of questionable or borderline results. Ideally, tests to measure serum MMA and homocysteine levels will become more readily available. Screening of the elderly asymptomatic population should be considered, as the initial signs and symptoms of cobalamin deficiency may be subtle.

Decreased Vitamin B_{12} Levels Due to Low Stomach Acidity

Vitamin B_{12} deficiency may correlate with conditions involving decreased stomach acidity because the protein-bound cobalamin must be separated by acid and pepsin. With aging, there is a gradual decrease in stomach acidity and therefore an increased chance of developing cobalamin deficiency. Since the introduction of H_2-receptor antagonists and proton pump inhibitors, however, the question of possible vitamin B_{12} malabsorption with these agents has been raised in populations of all ages. Streeter et al[20] found that small doses (400 mg/d) of cimetidine had no effect on vitamin B_{12} absorption, whereas larger doses (1000 mg/d) decreased food-bound vitamin B_{12} absorption to one third of the absorption level during periods without cimetidine. This was true both in patients with peptic ulcer and in normal, healthy controls. This finding was confirmed by Steinberg and associates,[21] who studied patients taking doses of 1200 mg/d and found vitamin B_{12} absorption reduced to 10% of baseline levels during a follow-up of 6 weeks. This effect was also demonstrated with ranitidine treatment of 300 mg/d, which caused a decrease in absorption to about 10% of baseline levels.[22] These results were not supported by a study by Hamburg et al[23] in which 20 healthy volunteers were fed a homogenate of liver paste. In a review on the subject, Force and Nahata[24] hypothesized that this procedure created free vitamin B_{12}, which would not require an acidic environment for absorption.

Omeprazole and lansoprazole are the first two of a new class of acid-reducing agents known as proton pump inhibitors. They cause a much more complete suppression of stomach acid, and therefore would be expected to have an even greater effect on food-bound vitamin B_{12} absorption. In the only study available for review, Marcuard et al[25] found that 20 mg/d of omeprazole reduced vitamin B_{12} absorption from 3.2% to 0.9%, and 40 mg/d reduced it from 3.4% to 0.4%.

Persons with the human immunodeficiency virus (HIV) are another key patient population in whom vitamin B_{12} malabsorption may not be routinely suspected. The HIV causes achlorhydria secondary to decreased secretion of acid and pepsin.[26] Patients with HIV also exhibit decreased secretion of intrinsic factor,[26] which would lead to an increased incidence of pernicious anemia. Therefore, patients with acquired immunodeficiency syndrome (AIDS) also should be considered for periodic screening for vitamin B_{12} levels.

In summary, it appears that maintenance doses or short-term treatment with normal doses of H_2-receptor antagonists would not cause vitamin B_{12} deficiency in a normal subject. As it takes 2 to 6 years for vitamin B_{12} deficiency due to dietary malabsorption to occur, long-term treatment with 300 mg/d or more of ranitidine, 1000 mg/d or more of cimetidine, or prolonged treatment with routine doses of omeprazole may cause vitamin B_{12} deficiency. All patients receiving long-term therapy with these medications should be considered for screening by vitamin B_{12} determinations. As patients with AIDS often end up with dementia associated with AIDS, it is important to rule out associated treatable causes of neuropsychiatric disorders, such as vitamin B_{12} deficiency, in this population.

Vitamin B_{12} and Dementia

As discussed previously, vitamin B_{12} deficiency can be manifested by neuropsychiatric difficulties including apparent dementia. As an overall cause of dementia, vitamin B_{12} deficiency is probably one of the least common. In a cohort study of over 400 nondemented elderly persons followed for several years, there was a 4.5% incidence of dementia in those with lower vitamin B_{12} levels and 7.5% in those with higher vitamin B_{12} levels. Unfortunately, no tests other than serum vitamin B_{12} levels were obtained, and the lower cutoff used was 150 μg/mL.[27] There were no further tests for borderline levels. It has become clear through studies by Martin and colleagues[28] that the length of time that vitamin B_{12}–dependent dementia exists untreated is important in prognostic determinations. Their study has shown that symptoms present for more than 12 months did not respond well to therapy, whereas dementias of shorter duration were quickly and remarkably reversed by vitamin B_{12} administration. Therefore, vitamin B_{12} levels should be ordered in all patients with dementia. Since dementia may have multiple causes, including new-onset vitamin B_{12} deficiency in patients with Alzheimer's disease, periodic screening should be considered throughout life in these patients.

Patients with HIV must also be evaluated for vitamin B_{12} deficiency, especially if there is an apparent dementia. In one recently published case report[29] a patient who was HIV-positive and assumed to have AIDS-related dementia was found to have low vitamin B_{12} levels. With replacement, this patient's mental status returned to baseline.

Table 3. Treatments for Vitamin B_{12} Deficiency

Method of Administration and Dosage	Monthly Cost, $
Intramuscular injection, 1000 μg once monthly	25.00
Oral tablets, 1000 μg daily	2.50
Intranasal gel, 400 μg/d 3 days per week	13.00

Vitamin B_{12} deficiency, however, does not appear to be a major causative factor in dementia of persons with AIDS, but probably plays a minor role. In a study of over 150 patients with AIDS,[30] the serum vitamin B_{12} levels were not significantly correlated with dementia. Again, only serum vitamin B_{12} levels were obtained, and no other testing was done.

In summary, all patients with dementia should have intermittent serum vitamin B_{12} levels determined at baseline and should be considered intermittently afterward. Patients with borderline results should probably have additional testing done, ie, MMA and homocysteine levels, as dementia resulting from cobalamin deficiency is best treated early.

Treatment

There is dispute about the treatment of vitamin B_{12} deficiency. Most textbooks recommend parenteral therapies with loading schedules ranging from 100 μg per week[31] to 1000 μg/d,[32] administered intramuscularly (IM). Maintenance dosages range from 100 μg[33] to 1000 μg per month IM.[34,35] One reason for the debate is that there are two cobalamin replacement agents, hydroxocobalamin and cyanocobalamin, available worldwide. Hydroxocobalamin, which is not available in the United States, is excreted more slowly than cyanocobalamin and could therefore be used in smaller dosages.[35] If parenteral therapy is used, we recommend 1000 μg per week IM for 4 weeks, then 1000 μg per month IM for life. This regimen is acceptable to most patients. It is reimbursable by third-party payers with appropriate diagnosis-related groups (DRG) coding (B_{12} deficiency, 266.2; atrophic gastritis, 535.1; macrocytic anemia, 281.9; neuropathy associated with deficiency, 266.2; pernicious anemia, 281.0).

Several reasons can be cited for our preference for treatment with 1000 μg per month IM. First, there is a generic product available for the higher dosage of cobalamin but not for the lower dosage. Second, older studies have shown that lower dosages are sometimes insufficient in keeping the serum levels over 200 pg/mL as there is a wide intrasubject response to replacement doses.[36] Also, previous research[37] has shown that there is a range of cobalamin requirements from 1.5 to 10 μg/d. Therefore, in some persons, a minimum dosage of 300 μg per month would be necessary. Lastly, there have been no reports in the medical literature of vitamin B_{12} toxicity, despite widespread use of higher dosages. Therefore, it seems prudent to ensure adequate replacement.

Despite the ease of parenteral replacement, the cost of office administration is approximately $25, and disposal of hazardous waste makes less invasive routes more desirable. Soon after the advent of replacement vitamin B_{12} for injection, oral formulations were developed. They were discontinued in the 1950s for a time because the original preparations contained animal intrinsic factor and were associated with antibody formation and a resulting relapse.[38] Oral formulations without intrinsic factor are now available, however, even in generic form. Complete success was noted in studies using 1000 μg/d of oral cobalamin. Normalization of serum levels, hematologic abnormalities, and symptoms was achieved in all 64 patients treated in one study.[39] In a recent editorial, Lederle[40] cited a survey he had done showing that 94% of internists were not aware of a cost-effective oral alternative to IM vitamin B_{12} injection. The dose of 1000 μg/d seems prudent, and serial vitamin B_{12} levels, as well as the decline of homocysteine and MMA levels, can be followed. If significant symptoms exist such as neurologic manifestations, therapy may be initiated intramuscularly and later switched to oral maintenance therapy. Daily oral treatment is much less expensive ($2.50) than once-a-month IM injection ($25.00) (Table 3).

Another possible alternative to parenteral therapy is the intranasal route of application, which may be useful if the patient does not respond to oral routes but does not desire parenteral routes. Romeo et al[41] have cited the anticipated approval by the Food and Drug Administration (FDA) of intranasal B_{12} for patients with vitamin B_{12} deficiency. At a dose of 500 μg per week, it was highly effective in reversing deficiencies. It was also compared with oral administration and was found to be significantly more bioavailable, delivering 1177 pg/mL through the intranasal route compared with 136 pg/mL delivered through the oral route after a single 500 μg dose.[41] At this time, it has not been approved by the FDA for widespread use. However, an intranasal gel is currently available, which is dosed at 400 μg three times per week.

Conclusions

Cobalamin deficiency may be more widespread than initially thought. Although once diagnosed, it is easy to treat, it is often not diagnosed early, causing unnecessary morbidity. General screening with vitamin B_{12} levels should be considered for all adults at age 65 years and possibly intermittently thereafter. Borderline levels should be pursued by testing MMA and homocysteine levels in

those with possible symptoms, or followed annually in asymptomatic adults for continued decline. Other high-risk persons who should be considered for screening for cobalamin deficiency include vegetarians, patients with partial or total gastrectomies or diseases of the small intestines, those with peripheral neuropathies, alcoholics, demented patients, and patients with HIV or AIDS. Therapy may be accomplished through monthly or bimonthly injections of 1000 μg if levels are stabilized, or by daily doses of 1000 μg orally under close supervision. Nasal preparations that would decrease the frequency of administration to once per week and offer alternatives to parenteral therapies if the oral route is not efficacious may soon be available.

Acknowledgment

Thanks to Jerry Spiegler for his assistance with this paper.

References

1. Food and Nutritional Board, National Research Council. Recommended daily allowances. 10th ed. Washington, DC: National Academy Press, 1989.
2. Kano Y, Sakamoto S, Miura Y, Takaku F. Disorders of cobalamin metabolism. Crit Rev Oncol Hematol 1985; 3:1–34.
3. Carethers M. Diagnosing vitamin B_{12} deficiency: a common geriatric disorder. Geriatrics 1988; 43:89–94, 105–7, 111–2.
4. Marcus DL, Shadick N, Crantz J, Gray M, Hernandez F, Freedman ML. Low serum B_{12} levels in a hematologically normal elderly subpopulation. J Am Geriatr Soc 1987; 35:635–8.
5. Pennypacker LC, Allen RH, Kelly JP, Matthews LM, Grigsby J, et al. High prevalance of cobalamin deficiency in elderly outpatients. J Am Geriatr Soc 1992; 40:1197–204.
6. Yao Y, Yao Sl, Yao SS, Yao G, Lou W. Prevalence of vitamin B_{12} deficiency among geriatric outpatients. J Fam Pract 1992; 35:524–8.
7. Clementz GL, Schade SG. The spectrum of vitamin B_{12} deficiency. Am Fam Physician 1990; 41:(1)150–62.
8. Lindenbaum J, Healton EB, Savage DG, et al. Neuropsychiatric disorders caused by cobalamin deficiency in the absence of anemia or macrocytosis. N Engl J Med 1988; 46:387–402.
9. Herbert V. Nutrition science as a continually unfolding story: the folate and vitamin B_{12} paradigm. The Herman Award Lecture. Am J Clin Nutr 1987; 46:387–402.
10. McRae TD, Freedman ML. Why vitamin B_{12} deficiency should be managed aggressively. Geriatrics 1989; 44:70–3, 76, 79.
11. Herbert V. Don't ignore low serum cobalamin (vitamin B_{12}) levels. Arch Intern Med 1988; 148:1705–7.
12. Yao Y, Yao G, Mesches DN, Lou W. Decline of serum cobalamin levels with increasing age among geriatric outpatients. Arch Fam Med 1994; 3:918–22.
13. Allen RH, Stabler SP, Savage DG, Lindenbaum J. Diagnosis of cobalamin deficiency I: Usefulness of serum methylmalonic acid and total homocysteine concentrations. Am J Hematol 1990; 34: 90–8.
14. Savage DG, Lindenbaum J, Stabler SP, Allen RH. Sensitivity of methylmalonic acid and total homocysteine determinations for diagnosing cobalamin and folate deficiencies. Am J Med 1994; 96: 239–46.
15. Waterbury L. Hematology for the house officer. Baltimore, Md: Williams & Wilkins, 1981: 18–27.
16. Nimo RE, Carmel R. Increased sensitivity of the detection of the blocking (type I) anti-intrinsic factor antibody. Am J Clin Pathol 1987; 88:729–33.
17. Fairbanks VF, Lennon VA, Kokmem E, Howard FM Jr. Tests for pernicious anemia: serum intrinsic factor antibody. Mayo Clin Proc 1983; 58:203–4.
18. Slingerland DW, Carderelli JA, Burrows BA, et al. The utility of serum gastrin levels in assessing the significance of low serum vitamin B_{12} levels. Arch Intern Med 1984; 144:1167–8.
19. Miller A, Slingerland DW, Cardarelli JA, Burrows BA, et al. Further studies on the use of serum gastrin levels in assessing the significance of low serum vitamin B_{12} levels. Am J Hematol 1989; 31:194–8.
20. Streeter AM, Goulston KJ, Bathur FA, Hilmer RS, Crane GG, Pheils MT. Cimetidine and malabsorption of cobalamin. Dig Dis Sci 1982; 27:13–6.
21. Steinberg WM, King CE, Toskes PP. Malabsorption of protein-bound cobalamin but not unbound cobalamin during cimetidine administration. Dig Dis Sci 1980; 25:188–92.
22. Belaiche J, Cattan D, Zittoun J, Marquet J, Yvart J. Effect of ranitidine on cobalamin absorption. Dig Dis Sci 1983; 26:667–8.
23. Hamborg B, Kittang F, Schjonsby H. The effect of ranitidine on the absorption of food cobalamins. Scand J Gastroenterol 1985; 20: 756–8.
24. Force RW, Nahata MC. Effect of histamine H_2-receptor antagonists on vitamin B_{12} absorption. Ann Pharmacother 1992; 26:1283–6.
25. Marcuard SP, Albernaz L, Prabhaker GK. Omeprazole therapy causes malabsorption of cyanocobalamin (vitamin B_{12}). Ann Intern Med 1994; 120:211–5.
26. Herzlich BC, Schiano TD, Moussa Z, Zimbalist E, Panagopolis G, et al. Decreased intrinsic factor secretion in AIDS: relation to parietal cell acid secretory capacity and vitamin B_{12} malabsorption. Am J Gastroenterol 1992; 87:1781–8.
27. Crystal HA, Ortof E, Frishman WN, Gruber A, Hershman D, Aronson M. Serum vitamin B_{12} levels and incidence of dementia in a healthy elderly population: a report from the Bronx longitudinal aging study. J Am Geriatr Soc 1994; 42:933–6.
28. Martin DC, Francis J, Protetch J, Huff FJ. Time dependency of cognitive recovery with cobalamin replacement: report of a pilot study. J Am Geriatr Soc 1992; 40:168–72.
29. Herzlich BC, Schiano TD. Reversal of apparent AIDS dementia complex following treatment with vitamin B_{12}. J Intern Med 1993; 233:495–7.
30. Robertson KR, Stern RA, Hall CD, Perkins DO, Wilkins JW. Vitamin B_{12} deficiency and the nervous system in HIV infection. Arch Neurol 1993; 50:807–11.
31. Hazzard WR, Andres R, Bierman EL, Blass JP. Principles of geriatric medicine and gerontology. New York, NY: McGraw-Hill, 1990.
32. Williams WJ, Beutler E, Erslev AJ, Lichtman MA. Hematology. 4th ed. New York, NY: McGraw-Hill, 1990.
33. Calkins E, Davis PJ, Ford A, eds. The practice of geriatrics. Philadelphia, Pa: WB Saunders, 1986:523.
34. Hoffman R, Benz EJ, Shattil SJ, et al, eds. Hematology: basic principles and practice. New York, NY: Churchill Livingstone, 1991.
35. Watts DT. Vitamin B_{12} replacement therapy: how much is enough? Wis Med J 1994; 5:203–5.
36. Chalmers JNM, Shinton NK. Comparison of hydroxocobalamin and cyanocobalamin in the treatment of pernicious anaemia. Lancet 1965; 7426:1305–8.
37. Adams JF, Boddy K. Metabolic equilibrium of tracer and natural vitamin B_{12}. Br J Lab Clin Med 1968; 72:392–6.
38. Lowenstein L, Cooper BA, Brunton L, Gartha S, Kerner K. An immunological basis for acquired resistance to oral administration of hog intrinsic factor and vitamin B_{12} in pernicious anemia. J Clin Invest 1961; 40:1656–62.
39. Berlin H, Berlin R, Brante G. Oral treatment of pernicious anaemia with high doses of vitamin B_{12} without intrinsic factor. Acta Med Scand 1968; 184:247–58.
40. Lederle FA. Oral cyanocobalamin for pernicious anemia: medicine's best kept secret? JAMA 1991; 265:94–5.
41. Romeo VD, Sileno A, Wenig DN. Intranasal cyanocobalamin [letter]. JAMA 1992; 268:1268.